REMARKS

Claims 1-27 are pending, claims 1-14 have been examined, and claims 15-27 are withdrawn pending a decision on whether re-joinder is deemed proper. Applicant submits that the claims are patentable as previously presented.

Rejection under 35 U.S.C. § 102(b)

Claims 1-5 and 10 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Dandiker et al. (US 5,425,950, hereafter "Dandiker"). The rejection is respectfully traversed. Dandiker does not disclose a "rapid release mantle, free of sumatriptan, wherein the mantle entirely surrounds the core."

It is respectfully submitted that the Examiner's characterization of the three layers of Dandiker's Example 10 tablets is mistaken. According to the examiner,

> Albeit true that Example 10 disclosed by Dandiker has three discrete layers of the following:
> I) a core containing sumatriptan;
> II) an immediate release coating free of sumatriptan; and
> III) a sustained release coating containing sumatriptan."

Office Action, paragraph bridging page 2-3. As explained below, layer II is not an immediate release coating, but rather an "Intermediate Polymer Layer" containing a pH-independent hydrophilic polymer. Likewise layer III is not a sustained release layer, but rather an immediate release layer. Dandiker col. 14, lines 59 and 66. According to Dandiker,

> For a fixed composition of outer layer and inner layer according to the invention, the release profile of the preparation will depend upon the thickness of the outer hydrophilic polymer coating.
>
> * * * * *
>
> Thus, in the case of sumatriptan the pharmaceutical compositions of the invention conveniently provide an immediate dose of

> sumatriptan followed by a further dose after a time-delay of 1 to 6 hours (e.g., 1 to 3.5 hours).

Dandiker, col. 7, lines 23-27; col. 8, lines 56-60.

It would be helpful at this point to pause and consider Dandiker's definitions of the terms "gradually" and "rapidly" as applied to rate of dissolution, and Dandiker's discussion of the role played by the pH independent hydrophilic polymer layer in delaying dissolution of the core. In Dandiker, "gradually" is understood as:

> When in the compositions according to the invention, a layer or layers is "gradually" removed, this means that the layer is removed over a time period of, for example, 1-8 hours, such as 1-3.5 hours, 2-5 hours or 4-6 hours following administration.

Dandiker, col. 5, lines 14-18 (emphasis added).

In Dandiker, "rapidly" is understood as:

> When in the compositions according to the invention, a layer or layers disintegrates "rapidly", this means that the layer disintegrates over a time period of, for example, less than 30 minutes, for example less than 10 minutes once exposed.

Dandiker, col. 5, lines 19-23 (emphasis added).

In Dandiker, a "pulsed release dosage form" is to be understood as "a dosage form which provides for rapid release of an active ingredient after an initial time delay." Dandiker col. 1, lines 49-53.

According to Dandiker, a pulsed release dosage form is achieved by covering the core with a polymer layer that is released only gradually:

> It will be appreciated that the rapidly disintegrating inner layer or layers in the compositions according to the invention will only start to disintegrate once the outer pH independent hydrophilic polymer layer has been removed to expose a portion or all of the inner layer.

> The term "pH independent hydrophilic polymer" will be well-understood by those skilled in the art. Such polymers dissolve/erode after administration at a rate which is independent of the pH of the surrounding fluid.

Dandiker, col. 5, lines 24-34 (emphasis added). According to Dandiker, "The pharmaceutical compositions of the [Dandiker] invention have the advantages associated with pulsed release, sustained release and/or delayed release dosage forms", Dandiker, col. 2, lines 48-50; and "[t]he pharmaceutical compositions of the [Dandiker] invention are also able to provide a distinct pulse with no premature leakage of the active ingredient from the core". Dandiker, col. 3, lines 3-5.

The tablets set forth in Example 10 are thus better understood in light of Dandiker's discussion of the concepts of 'gradual', 'rapid', and 'pulsed' release' outlined above. According to Dandiker, the tablets of Example 10 have three layers:

> In a preferred or alternative aspect the invention also provides a pharmaceutical composition comprising:
> (a) an outer layer comprising a pH independent hydrophilic polymer together with one or more fillers;
> (b) an inner core comprising sumatriptan;
> wherein the outer layer is gradually removed by a combination of dissolution and erosion following administration and the inner core disintegrates rapidly once exposed.
> In a preferred or alternative aspect the sumatriptan containing pharmaceutical compositions of the invention are additionally provided with a rapidly disintegrating outer coating, surrounding the pH independent hydrophilic polymer layer, comprising sumatriptan to provide an immediate release of drug.

Dandiker col. 4, line 61 to col. 5, line 8) (emphasis added). In contrast to the examiner's characterization, the three layers are more accurately summarized as:

I. a "Tablet Core", containing sumatriptan (3.0 mm diameter);

II. an "Intermediate Polymer Layer" (either 5.7 mm or 8.0 mm); and

III. an "Outer Sumatriptan Layer".

According to Dandiker, layer III has the "same formulation as the core tablet" (col. 14, line 50), which formulation results in immediate release of sumatriptan (col. 14, line 59). Dandiker states that layer II, the "Intermediate Polymer Layer", required 1.5 hours to dissolve when applied at a thickness of 5.7 mm[1] (hereafter "tablet 10(a)"), and required 3 hours to dissolve when applied at a thickness of 8.0 mm[2](hereafter "tablet 10(b)"). Dandiker, col. 14, lines 59-68. Being within the range of 1-6 hours, the rate of dissolution of the intermediate polymer layer would be considered gradual, not rapid, according to Dandiker's own definitions of those terms.

Similarly, Dandiker at col. 14, lines 59-61, states that tablet 10(a) delivers immediate release of sumatriptin (by rapid dissolution of the Outer Sumatriptin Layer (Layer III)), followed by a pulsed release of sumatriptan (a 1.5 hour delay to dissolve the sumatriptin-free Intermediate Polymer Layer (Layer II) followed by rapid dissolution of the sumatriptan-containing Tablet Core (Layer I); *see*, definition of "pulsed release" above and at Dandiker col. 1, lines 49-53).

Moreover, Dandiker at col. 14, lines 66-68, states that tablet 10(b) delivers immediate release of sumatriptin (by rapid dissolution of the Outer Sumatriptin Layer (Layer III)), followed by a pulsed release of sumatriptan (a 1.5 hour delay to dissolve the sumatriptin-free Intermediate Polymer Layer (Layer II) followed by rapid dissolution of the sumatriptan-containing Tablet Core (Layer I); *see*, definition of "pulsed release" above and at Dandiker col. 1, lines 49-53).

Thus, Dandiker describes a tablet having an intermediate layer comprising a pH independent hydrophilic polymer and an inner layer or layers each comprising an active

[1] 8.7 mm diameters minus 3.0 mm diameter core
[2] 11.0 mm diameter minus 3.0 mm core

sumatriptan ingredient. The intermediate layer is gradually removed by a combination of dissolution and erosion following administration (column 3, lines 17-28). The tablet is designed to provide a pulsed release or delayed sustained release of the active ingredient from the core (column 2, lines 23-24; column 3, lines 3-7). Thus, layer II is not an immediate release coating as stated by the examiner, but rather an "Intermediate Polymer Layer" containing a pH-independent hydrophilic polymer that dissolves with the delay necessary to provide a pulsed release dosage form. The intermediate layer of Dandiker is never rapid-release (in contrast to the mantle of the tablets of the present invention) - if it was, the delayed sustained or delayed pulsed release of drug from the core of the Dandiker tablets would be compromised. This is confirmed e.g. at col. 9, lines 39-41, which stress the importance of rapid wetting of the intermediate layer to form a gel (effectively a barrier to drug diffusion from the core through the intermediate layer) in order to prevent "premature" drug release from the core. (See also e.g. col. 3, lines 17-28, for the slow erosion/dissolution of the intermediate layer.) Thus, the Examples of Dandiker all confirm that the release of drug from the core occurs gradually over several hours.

In contrast, claims 1 and 5-10 are directed to providing a tablet preparation that comprises a core containing sumatriptan and a rapid-release mantle, free of sumatriptan, which entirely surrounds the core. Such tablets are not described by Dandiker because the polymer containing intermediate layer of Dandiker is removed only gradually, not rapidly as required by claims 1-5 and 10. Thus, the claimed subject matter is distinguished from Dandiker by the fact that the instant mantle is a rapid release mantle.and the rejection should be withdrawn.

Turning to the examiner's comments regarding instant claim 5, Dandiker states that:

> In designing dosage forms according to the [Dandiker] invention in order to tailor the rate and manner of release of the active ingredients, certain factors are important and such factors include: 1. Polymer hydration rates. . . 2. Particle size. . . . 3. Polymer solution viscosity. . . .4. Polymer concentration. . . . 5. Presence of soluble/insoluble and swelling/nonswelling fillers. . . . 6. Presence of surfactants and ionic salts. . . . [and] 7. Thickness of the outer polymer layer.

Dandiker col. 9 line 30 to col. 10, line 68. Applicants further direct the examiner's attention to the list of ingredients for Dandiker's "Tablet Core" and "Intermediate Polymer Layer". Dandiker col. 14 lines 20-25, and col. 14 lines 36-44, respectively. The formulation of the Tablet core is designed to be immediate release. The formulation of the Intermediate Polymer Layer is designed for a delayed rate of dissolution/erosion. Thus, the core and intermediate layer of Dandiker do not comprise substantially the same materials. It is respectfully requested that the rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 1-5 and 10-14 have been rejected under 35 U.S.C. § 103(a) as not being patentable over Dandiker et al. (US 5,425,950), in view of Lerner et al. (US 2004/0052843, "Lerner"). The rejection is respectfully traversed. The claimed invention is not obvious in view of the combination of Dandiker and Lerner.

The arguments provided above in response to the Examiner's 35 U.S.C. § 102(b) rejection establish that the tablets of Dandiker do not include a rapid release mantle, free of sumatropin, which entirely surrounds the core. Moreover, Dandiker is directed to tablets that provide a pulsed release or delayed sustained release of a drug from the core, by surrounding the core with a gradually eroding layer (e.g. the "Intermediate Polymer Layer" of Example 10 of Dandiker).

The examiner alleges that it would have been obvious to combine the teachings of Dandiker and Lerner to "arriv[e] at a tablet comprising a core comprising sumatriptan and mantle free of sumatriptan where the weight ratio of the mantle to the core is less than 1.5:1." Office Action at page 8.

The transition from the pulsed release intermediate layer of Dandiker's Example 10, to the rapid release mantle layer of claim 1 is not a matter of routine optimisation, as alleged by the Examiner. Rather, the present invention provides a fundamentally different type of tablet in which the mantle and the core dissolve rapidly in the stomach to provide rapid delivery of the entire drug dose. Hence, the person of ordinary skill in the art, seeking to provide such a tablet to achieve rapid drug delivery, would not start from with a prior art reference relating to pulsed rate, and hence delayed, drug delivery.

Even if the teaching of Dandiker and Lerner were combined, this still would not have led the skilled person to the claimed invention. Lerner teaches a tablet in which the annular body dissolves more slowly than the core (paragraph [0051]) and in which drug release from the core is via the exposed surfaces not covered by the annular body. In fact, the examiner has "acknowleged that Lerner teaches a tablet wherein the coating layer does not entirely coat the drug containing core." Office Action at page 4, paragraph 12. Thus, neither Dandiker nor Lerner advocate a rapid release mantle which surrounds the core, as required by claim 1. Furthermore, if a person of ordinary skill in the art were to modify the teaching of Dandiker in view of Lerner in order to achieve rapid drug release, he would be directed by Lerner to do so by removing part of the intermediate layer of the Dandiker tablet so as to expose the core, not by modifying the composition of the intermediate layer of the Dandiker tablet in a way that is not taught or motivated by the disclosures of either Dandiker or Lerner. Combining Dandiker

and Lerner would not therefore lead to the claimed tablet comprising a core containing sumatriptan and a rapid release mantle, free of sumatriptan, wherein the mantle entirely surrounds the core.

Moreover, as noted in the previous response, neither Dandiker nor Lerner provides the combination of rapid release of sumatriptan and adequate taste masking provided by the tablets of the invention. Lerner advocates tablets for immediate release in which the active ingredient is released through the exposed surfaces of the core by dissolution in the saliva (see paragraph [0048] of Lerner). Such saliva-mediated release of the active ingredient cannot conceivably provide the taste masking achieved by the tablets of any one of claims 1-5 and 10-14. Thus, one of ordinary skill in the art familiar with Dandiker in view of Lerner would not be motivated to provide a tablet that fails to achieve the objective of masking unpleasant tastes. In light of this, it will be apparent that the skilled artisan, seeking to fulfil the object of providing an oral tablet preparation of sumatriptan, wherein the unpleasant taste of sumatriptan is masked and wherein release of sumatriptan from the tablet core is rapid (see specification, page 3, lines 28-31) would not have arrived at the claimed subject matter in an obvious manner in light of the content of Dandiker and Lerner.

In view of the deficiencies of both Dandiker and Lerner, the claimed subject matter cannot be regarded as obvious in light of those documents. It is respectfully requested that the rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 1 and 5-9 have been rejected under 35 U.S.C. § 103(a) as not being patentable over Dandiker et al. (US 5425950), in view of Lieberman et al. (Pharma. Dosage Forms Vol. 1:

tablets, 2nd edition, 1990, pp. 188-189) (hereafter "Lieberman"). The rejection is respectfully traversed.

The examiner begins with the premise that Dandiker discloses a sumatriptin core surrounded entirely by a sumatriptin-free mantle. But Dandiker fails to disclose a sumatriptin-free mantle that is rapid release. Instant claims 6-9 incorporate by reference the limitations of claim 1, and thus require that the tablet comprise a mantle which is a rapid release mantle, that the mantle be free of sumatriptan, and that it surround the core.

The examiner further attributes to Example 10 of Dandiker a core containing 23% microcrystalline cellulose as a filler, and an additional 23% microcrystalline cellulose as a disintegrant. This is not accurate. Example 10 of Dandiker disclosures a core that is 50% sumatriptin, 23% microcrystalline cellulose, and 23% lactose.

Lieberman consists of a two page excerpt which the examiner alleges to have been copied from the first volume of Pharma. Dosage Forms.[3] The first two paragraphs of page 188 discuss the preparation of drugs in prolonged (not rapid) release form by means of synthetic resins, aluminum hydroxide, clays, and ionic exchange resins. Under the title "VIII. Manufacturing Problems", the remainder of pages 188-89 is directed to the complexities of using tablet presses to manufacture tablets. Such problems include: A) insufficient lubrication leading to binding in the die or difficult ejection; B) sticking, picking, and filming, which the author attributes to improperly dried or lubricated granulation causing the tablet surface to stick to the punch faces; and C) capping and laminating, which occur when the upper segment of the

[3] For the record, the copy of the Lieberman reference enclosed with the office action consisted of only pages 188-89; notably, the front and back of the title page and table of contents were not included as part of the reference copy. Thus, the reference copy does not include the pages exhibiting the author, title, or date, nor any other information required for an adequate citation. Thus, the reference copy lacks information on which to verify the accuracy of the examiner's citation.

tablet separates from the main portion of the tablet and comes off as a cap, or comes apart at the sides, respectively.

The Lieberman reference fails to teach or even suggest the rapid release, sumatriptin-free mantle lacking in the Dandiker reference. Nor would one skilled in the art derive any motivation from Lieberman for making and using a rapid release, sumatriptin-free mantle. Thus, the examiner has not established a *prima facie* case of obviousness. Claims 1 and 5-9 cannot be considered to be obvious in light of Dandiker and Lieberman. The Examiner's objection should be withdrawn.

CONCLUSION

Please charge any outstanding fees or credit any overpayments to Deposit Account No. 50-1895, Ref. No. 0765-005US1.

Respectfully submitted:

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